Amendments to the Specification:

Please amend the specification as set forth hereinafter:

On page 4, please amend the paragraph starting on line 24 as follows:

-- These and other objects are achieved by the present invention, which provides a method ~~according to claim 1~~ as set forth herein, a kit for detecting interactions between either two membrane proteins or one membrane and one cytosolic protein ~~according to claim 9~~ as set forth herein, and vectors ~~according to claim 18 and 32~~ as set forth herein. The method is based on the reconstitution of a protein involved in intracellular protein degradation, such as ubiquitin and which makes use of chimeric genes, which express hybrid proteins. Two types of hybrid proteins are prepared. The first hybrid contains a membrane protein of interest (bait) fused to e.g. the CbM-TDA module (containing C-terminal domain of ubiquitin (CbM) followed e.g. by an artificial transcriptional activator (e.g. LexM-B42)). The second hybrid protein (prey) contains e.g. an N-terminal domain of ubiquitin (NbM) fused to the second test protein. The prey protein can be either a membrane protein or a soluble cytoplasmic protein. If two test proteins are able to interact, they reconstitute two separate ubiquitin domains into an active ubiquitin leading to the cleavage of the transcriptional activator and activation of the reporter system. --

On page 23, please amend the paragraph starting on line 26 as follows:

-- (2) A nucleic acid sequence encoding a leader which may be a signal sequence derived from a yeast integral membrane protein such as STE2 (Overton & Blumer, 2000) or a signal sequence which confers fatty acid modification to the following polypeptide (N-MGCTLSAEDKPGGP-C) (SEQ ID No. 1) which is in the same reading frame as the reading frame of the signal sequence (Angermayr et al., 2000, Wolven et al., 1997). --

On page 26, please amend the paragraph starting on line 1 as follows:

-- (3) pMP-CbM-TDA is a low copy yeast/E. coli shuttle vector carrying a CYC1 promoter for low level expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest. The multiple cloning site is followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding the 3xMYC epitope, followed by the sequence encoding the bacterial LexM protein, followed by the sequence encoding the *Herpes simplex* virus VP16 protein, followed by a CYC1 terminator. The backbone of the plasmid contains the LEU2 gene for selection in yeast, the

kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the low level expression of CbM-fused polypetides in yeast, due to the combination of a weak CYC1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the plasmid in yeast (usually 1-2 copies per cell). --

On page 27, please amend the paragraph starting on line 1 as follows:

-- (5) pMP-CbM-TDA is a low copy yeast/E. coli shuttle vector carrying a CYC1 promoter for low level expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest. The multiple cloning site is followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding the 3xMYC epitope, followed by the sequence encoding the bacterial LexM protein, followed by the sequence encoding the *Herpes simplex* virus VP16 protein, followed by a CYC1 terminator. The backbone of the construct contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the low level expression of CbM-fused polypeptides in yeast, due to the combination of a weak CYC1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the construct in yeast (usually 1-2 copies per cell). --

On page 27, please amend the paragraph starting on line 17 as follows:

-- (6) pCUP1-MP-CbM-TDA is a low copy yeast/E. coli shuttle vector carrying a CUP1 promoter for inducible expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest. The multiple cloning site is followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding the 3xMYC epitope, followed by the sequence encoding the bacterial LexM protein, followed by the sequence encoding the *Herpes simplex* virus VP16 protein, followed by a CYC1 terminator. The backbone of the construct contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the inducible expression of CbM-fused polypetides in yeast, due to the combination of an

inducible CUP1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the construct in yeast (usually 1-2 copies per cell). --

On page 30, please amend the paragraph starting on line 31 as follows:

-- (12) pMGA93B42 is a low copy yeast/E. coli shuttle vector carrying a CYC1 promoter for low level expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest. The multiple cloning site is followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding amino acids 1-93 of the yeast Gal4 protein, followed by the sequence encoding the acidic domain B42, followed by an ADH1 terminator. The backbone of the plasmid contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the low level expression of CbM-fused polypetides in yeast, due to the combination of a weak CYC1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the plasmid in yeast (usually 1-2 copies per cell). –

On page 31, please amend the paragraph starting on line 14 as follows:

-- (13) pMGA74B42 is a low copy yeast/E. coli shuttle vector carrying a CYC1 promoter for low level expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest. The multiple cloning site is followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding amino acids 1-74 of the yeast Gal4 protein, followed by the sequence encoding the acidic domain B42, followed by an ADH1 terminator. The backbone of the plasmid contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the low level expression of CbM-fused polypetides in yeast, due to the combination of a weak CYC1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the plasmid in yeast (usually 1-2 copies per cell). This vector allows high stringency screens thanks to the use of a severely truncated Gal4 protein. Gal4 amino acids 1-74 retains the minimal elements necessary for recognition and binding to the GAL promoter, but it lacks the elements necessary for dimerization of the Gal4 protein. Therefore, binding of Gal4 amino acids 1-74 to the GAL1 promoter is not cooperative anymore. The non-cooperative mode of binding severely

reduces the affinity of Gal4 amino acids 1-74 for the GAL1 promoter as compared to Gal4 amino acids 1-93. Consequently, higher levels of Gal4 amino acids 1-74 are needed in the nucleus to activate transcription of the reporter genes. This higher level can only be reached by an overall higher level of released Gal4 (amino acids 1-74)-B42. Only a very strong interaction between a bait protein and a prey protein is able to release the amounts of Gal4 (amino acids 1-74)-B42 needed to activate transcription of the reporter genes. --

On page 32, please amend the paragraph starting on line 8 as follows:

-- (14) pCMGA93B42 is a low copy yeast/E. coli shuttle vector carrying a CUP1 promoter for inducible expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest. The multiple cloning site is followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding amino acids 1-93 of the yeast Gal4 protein, followed by the sequence encoding the acidic domain B42, followed by an ADH1 terminator. The backbone of the plasmid contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the inducible expression of CbM-fused polypetides in yeast, due to the combination of an inducible CUP1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the plasmid in yeast (usually 1-2 copies per cell). --

On page 32, please amend the paragraph starting on line 23 as follows:

-- (15) pCMGA74B42 is a low copy yeast/E. coli shuttle vector carrying a CUP1 promoter for inducible expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest. The multiple cloning site is followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding amino acids 1-74 of the yeast Gal4 protein, followed by the sequence encoding the acidic domain B42, followed by an ADH1 terminator. The backbone of the plasmid contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the inducible expression of CbM-fused polypetides in yeast, due to the combination of an inducible CUP1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the plasmid in yeast (usually 1-2 copies per cell). This vector

allows high stringency screens thanks to the use of a severely truncated Gal4 protein. Gal4 amino acids 1-74 retains the minimal elements necessary for recognition and binding to the GAL promoter, but it lacks the elements necessary for dimerization of the Gal4 protein. Therefore, binding of Gal4 amino acids 1-74 to the GAL1 promoter is not cooperative anymore. The non-cooperative mode of binding severely reduces the affinity of Gal4 amino acids 1-74 for the GAL1 promoter as compared to Gal4 amino acids 1-93. Consequently, higher levels of Gal4 amino acids 1-74 are needed in the nucleus to activate transcription of the reporter genes. This higher level can only be reached by an overall higher level of released Gal4 (amino acids 1-74)-B42. Only a very strong interaction between a bait protein and a prey protein is able to release the amounts of Gal4 (amino acids 1-74)-B42 needed to activate transcription of the reporter genes. --

On page 33, please amend the paragraph starting on line 17 as follows:

-- (16) pMP-CbM-ML-MCS is a low copy yeast/E. coli shuttle vector carrying a CYC1 promoter for low level expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding the 3xMYC epitope, followed by the sequence encoding the bacterial LexM protein, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest, followed by a CYC1 terminator. The backbone of the construct contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the low level expression of CbM-fused polypetides in yeast, due to the combination of a weak CYC1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the construct in yeast (usually 1-2 copies per cell). --

On page 34, please amend the paragraph starting on line 1 as follows:

-- (17) pCUP1-MP-CbM-ML-MCS is a low copy yeast/E. coli shuttle vector carrying a CUP1 promoter for inducible expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding the 3xMYC epitope, followed by the sequence encoding the bacterial LexM protein, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest, followed by a CYC1 terminator. The backbone of the construct contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for

propagation in yeast and the pUC origin of replication for propagation in E. coli. replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the inducible expression of CbM-fused polypetides in yeast, due to the combination of an inducible CUP1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the construct in yeast (usually 1-2 copies per cell). --

On page 34, please amend the paragraph starting on line 17 as follows:

-- (18) pMGA93-MCS is a low copy yeast/E. coli shuttle vector carrying a CYC1 promoter for low level expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding amino acids 1-93 of the yeast Gal4 protein, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest, followed by an ADH1 terminator. The backbone of the construct contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the low level expression of CbM-fused polypetides in yeast, due to the combination of a weak CYC1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the construct in yeast (usually 1-2 copies per cell). --

On page 34, please amend the paragraph starting on line 31 as follows:

-- (19) pMGA74-MCS is a low copy yeast/E. coli shuttle vector carrying a CYC1 promoter for low level expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding amino acids 1-74 of the yeast Gal4 protein, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest, followed by an ADH1 terminator. The backbone of the construct contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the low level expression of CbM-fused polypetides in yeast, due to the combination of a weak CYC1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the construct in yeast (usually 1-2 copies per cell). This vector allows high stringency screens thanks to the use of a severely truncated Gal4 protein. Gal4 amino acids 1-74 retains the minimal elements necessary for recognition and binding to the GAL promoter, but it lacks the elements necessary for dimerization of tge Gal4 protein. Therefore, binding of Gal4 amino acids

1-74 to the GAL1 promoter is not cooperative anymore. The non-cooperative mode of binding severely reduces the affinity of Gal4 amino acids 1-74 for the GAL1 promoter as compared to Gal4 amino acids 1-93. Consequently, higher levels of Gal4 amino acids 1-74 are needed in the nucleus to activate transcription of the reporter genes. This higher level can only be reached by an overall higher level of released Gal4 (amino acids 1-74)-bait polypeptide. Only a very strong interaction between a bait protein and a prey protein is able to release the amounts of Gal4 (amino acids 1-74)-bait polypeptide needed to activate transcription of the reporter genes. --

On page 35, please amend the paragraph starting on line 25 as follows:

-- (20) pCMGA93-MCS is a low copy yeast/E. coli shuttle vector carrying a CUP1 promoter for inducible expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding amino acids 1-93 of the yeast Gal4 protein, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest, followed by an ADH1 terminator. The backbone of the construct contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the inducible expression of CbM-fused polypetides in yeast, due to the combination of an inducible CUP1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the construct in yeast (usually 1-2 copies per cell). --

On page 36, please amend the paragraph starting on line 8 as follows:

-- (21) pCMGA74-MCS is a low copy yeast/E. coli shuttle vector carrying a CUP1 promoter for inducible expression in yeast, followed by a nucleic acid sequence encoding the N-MGCTLSAEDKPGGP-C (SEQ ID No. 1) signal sequence for fatty acid modification, followed by a nucleic acid sequence encoding amino acids 35-76 of yeast ubiquitin (CbM), followed by a sequence encoding amino acids 1-74 of the yeast Gal4 protein, followed by a multiple cloning site encoding several recognition sites for restriction endonucleases, which can be used to insert a nucleic acid encoding the polypeptide of interest, followed by an ADH1 terminator. The backbone of the construct contains the LEU2 gene for selection in yeast, the kanamycine resistance cassette for selection in E. coli, the CEN/ARS origin of replication for propagation in yeast and the pUC origin of replication for propagation in E. coli. This vector is suitable for the inducible expression of CbM-fused polypetides in yeast, due to the combination of an inducible CUP1 promoter and a CEN/ARS origin of replication, which results in low copy numbers of the construct in yeast (usually 1-2 copies per cell). This vector allows high stringency screens thanks to the use of a severely truncated Gal4 protein. Gal4 amino

acids 1-74 retains the minimal elements necessary for recognition and binding to the GAL promoter, but it lacks the elements necessary for dimerization of tge Gal4 protein. Therefore, binding of Gal4 amino acids 1-74 to the GAL1 promoter is not cooperative anymore. The non-cooperative mode of binding severely reduces the affinity of Gal4 amino acids 1-74 for the GAL1 promoter as compared to Gal4 amino acids 1-93. Consequently, higher levels of Gal4 amino acids 1-74 are needed in the nucleus to activate transcription of the reporter genes. This higher level can only be reached by an overall higher level of released Gal4 (amino acids 1-74)-bait polypeptide. Only a very strong interaction between a bait protein and a prey protein is able to release the amounts of Gal4 (amino acids 1-74)-bait polypeptide needed to activate transcription of the reporter genes. --